BRCA1 discovery to precision oncology: The road ahead

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Statement of the Problem: Breast cancer is the second leading cause of cancer-related deaths among women. BRCA1 mutations results in triple negative breast cancer (TNBC) and high grade serous ovarian cancer HGSOC. Majority of young AA women with BRCA1 mutations have a so-called TNBC with an aggressive phenotype. Currently there is no targeted therapy for TNBC. Our group has reported BRCA1 proteins, unlike the disease-associated proteins to interact with a druggable target Ubc9 which facilitates both the entry of BRCA1 proteins into the nucleus to cause ubiquitination of ER and TNBC tumor suppression. Many BRCA1 missense mutant alleles, termed variants of uncertain significance (VUS) are difficult to classify as benign or malignant. Therefore for a woman who carries a BRCA1 VUS allele, the risk of developing TNBC is unknown.

Hypothesis and Methodology: This work is based on the hypothesis that BRCA1 is a tumor suppressor gene and its coding region can harbor several mutations some of which are driver mutations and others passenger mutations similar to WT BRCA1. We tested this hypothesis by studying the various biological functions of BRCA1 mutant proteins so as to identify the driver mutations that lead to these TNBC.

Conclusion and Significance: Clinically, the ability to predict which of these are driver mutations that can result in TNBC offers unprecedented prospects for early detection to make informed decisions regarding prophylactic measures. The results from this study will stratify the risk for TNBC as well as develop personalized targeted therapy for women with BRCA1-associated TNBC thus reducing the mortality associated with these cancers to achieve health equity for all.

Speaker Biography

Veena N Rao is Professor and Co-Director of the Cancer Biology Program, GCC Distinguished Cancer Scholar in the Department of OB/GYN, at Morehouse School of Medicine. She has completed her PhD in Biochemistry at CCMB, India, Max Planck Institute, University of Edinburgh, and MIT, Boston. She did her postdoctoral work at the University of California, Yale University and National Cancer Institute. She has a long career beginning at University of Pennsylvania, Temple University as an Assistant Professor. She then moved to Thomas Jefferson University as Associate Professor where she identified the BRCA1 isoforms. She became Professor and Co-Director of the Division of Cancer Genetics at Drexel University and was recruited at Morehouse School of Medicine to train minority students in cancer research. Her work led to a patent that can stratify risk for TNBC and to develop targeted therapy for TNBC, a disease which currently has no targeted treatments available.

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